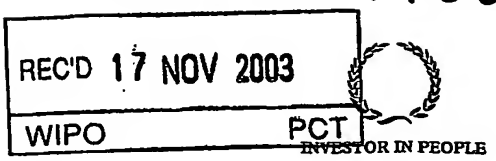
PCT/EP03/11650



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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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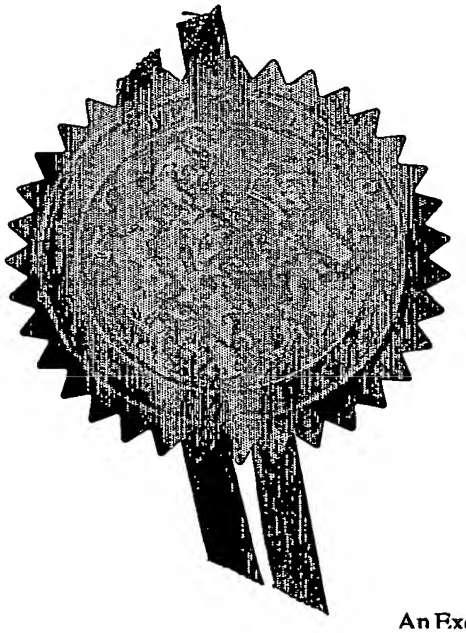

Signed Stephen Hordley

Dated 12 September 2003

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20MAR03 E793634-1 D02029
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The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — MG/PMS/P33128P1

2. Patent application number
(The Patent Office will fill in his part) — 0306328.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom 07358708

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* — 80725550006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
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Continuation sheets of this form	0
Description	24
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Drawings	0

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature M Gibson Date 19-Mar-03

12. Name and daytime telephone number of person to contact in the United Kingdom: M Gibson 01279 644841

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P33128P1

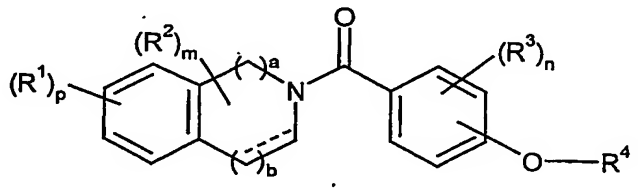
NOVEL COMPOUNDS

The present invention relates to novel bicyclic benzamide derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

WO 02/76925 (Eli Lilly), WO 00/06254 (Societe Civile Bioprojet) and WO 01/66534 (Abbott Laboratories) describe a series of compounds which are claimed to be histamine H3 antagonists.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists such as the current series could be useful for the treatment of cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, aryl, heteroaryl, heterocyclyl, arylC_{1-6} alkyl, heteroarylC_{1-6} alkyl,

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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

United Kingdom

07358705

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

heterocyclylC_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, -CO-aryl, -CO-heterocyclyl, -CO-heteroaryl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylaminosulfonyl, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $NR^{15}R^{16}$, $-NR^{15}CO$-aryl, $-NR^{15}CO$-heterocyclyl, $-NR^{15}CO$-heteroaryl, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-NR^{15}SO_2R^{16}$ or $-SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl; wherein said aryl, heteroaryl and heterocyclyl groups of R^1 and R^2 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different and which are selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, CF_3, OCF_3, CN, C_{1-6} alkanoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylamido or C_{1-6} alkylsulfonamido;

a and b independently represent 0, 1 or 2;

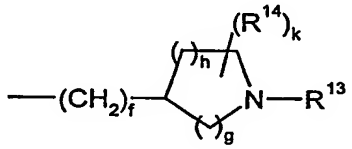
====== is a single or double bond;

R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

m and n independently represent 0, 1 or 2;

p represents an integer from 0 to 3, such that when p is an integer greater than 1, two R^1 groups may instead be linked to form a heterocyclyl group;

R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group optionally substituted by one or two R^{17} groups;

R^{13} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-aryl or heterocyclyl;

R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, OH, diC_{1-6} alkylamino or C_{1-6} alkoxy;

f and k independently represent 0, 1 or 2;

g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;

or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine and the term 'polyhalo' is used herein to refer to a moiety containing more than one (eg. 2-5) of said halogen atoms.

The term "aryl" includes phenyl and naphthyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 heteroatoms selected from oxygen or nitrogen. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,3-dioxolane, diazepanyl and azepanyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, m represents 0 or 1, more preferably 0.
Preferably, p represents 0, 1 or 2, more preferably 0 or 1.
When present, R^1 is preferably halogen (eg. fluorine, bromine or chlorine), hydroxy, cyano, nitro, $-NR^{15}R^{16}$ (eg. NH_2), $-NR^{15}COR^{16}$ (eg. -NH-acetyl), polyhaloC_{1-6} alkyl (eg. CF_3), heterocyclyl (eg. pyrrolidinyl optionally substituted by one or two oxo groups), C_{1-6} alkyl (eg. methyl), C_{1-6} alkoxy (eg. methoxy), C_{1-6} alkylsulfonyl (eg. $-SO_2Me$), C_{1-6} alkylsulfinyl (eg. –SOMe), C_{1-6} alkanoyl (eg. –COMe), arylsulfonamido (eg. $-NHSO_2Ph$), arylaminosulfonyl (eg. $-SO_2NHPh$) or $-NR^{15}SO_2R^{16}$ (eg. $-NHSO_2Me$).
In one preferred embodiment, p represents 2 and both R^1 groups are linked to form a heterocyclyl group (eg. 1,3-dioxolane).
When present, R^1 is more preferably halogen (eg. fluorine) or cyano.
When present, R^2 is preferably C_{1-6} alkyl (eg. methyl), arylC_{1-6} alkyl (eg. benzyl), aryl (eg. phenyl optionally substituted by one or more OMe or isopropylSO_2 groups) or heteroaryl (eg. thienyl).
When present, R^3 is preferably polyhaloC_{1-6} alkyl (eg. 2-CF_3).
When b is 0, a is preferably 1, when b is 1, a is preferably 0, 1 or 2 and when b is 2, a is preferably 0.
More preferred compounds of formula (I) are those wherein a is 1 and b is 0 or 1.
Preferably, ------ is a single bond.
Preferably, n represents 0 or 1, more preferably 0.
Preferably, R^4 represents $-(CH_2)_q-NR^{11}R^{12}$.
Preferably, q is 3.
Preferably, $NR^{11}R^{12}$ represents a heterocyclic group, more preferably unsubstituted piperidine.

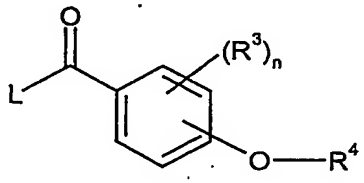
Preferred compounds according to the invention include examples E1-E49 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of histamine H3 receptor antagonists therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

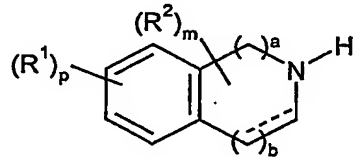
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

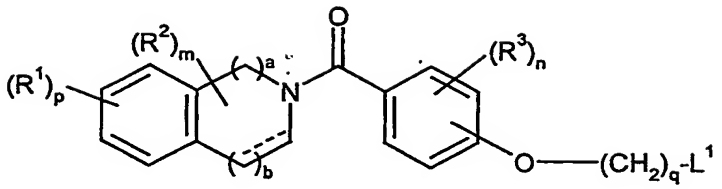
with a compound of formula (III)



(III)

or a protected derivative thereof, wherein R^1, R^2, R^3, R^4, a, b, m, n and p are as defined above and L is OH or a suitable leaving group (eg. a halogen atom such as chlorine); or

(b) preparing a compound of formula (I) wherein R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (IV)



(IV)

wherein R^1, R^2, R^3, a, b, m, n, p and q are as defined above and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; and optionally thereafter

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion to other compounds of formula (I).

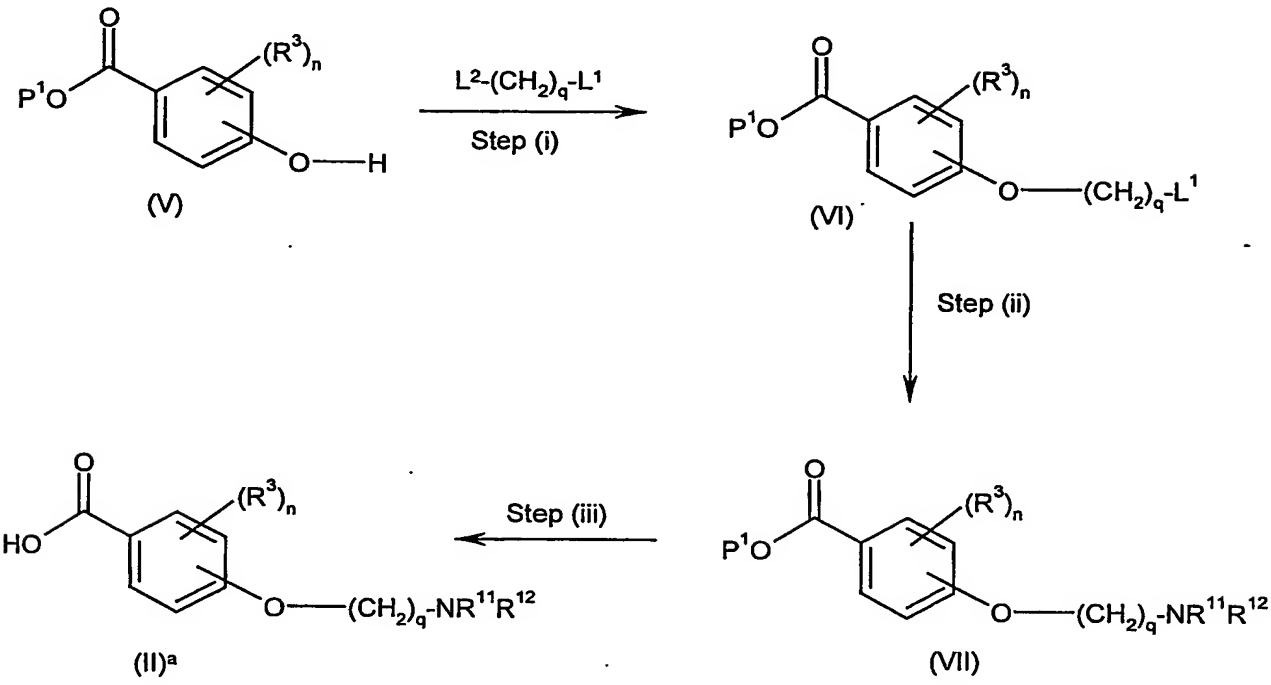
Process (a) typically comprises halogenation of the compound of formula (II) with a suitable halogenating agent (eg. thionyl chloride) followed by reaction with the compound of formula (III) in the presence of a suitable base such as triethylamine or a solid supported amine, in a suitable solvent such as dichloromethane. Process (a) may also typically comprise activation of the compound of formula (II) with a coupling reagent such as dicyclohexylcarbodiimide or solid supported carbodiimide in a suitable solvent such as N,N-dimethylformamide followed by reaction with the compound of formula (III).

Process (b) is typically performed in the presence of a suitable solvent (such as 1-butanol) at an elevated temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

Compounds of formula (II) wherein R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ may be prepared in accordance with the following procedure:



wherein R^3, n, q, R^{11} and R^{12} are as defined above, P^1 represents a protecting group such as methyl, ethyl or t-butyl, L^1 and L^2 independently represent a leaving group such as halogen (eg. L^1 represents chlorine and L^2 represents bromine). The $-CO_2H$ group of compounds of formula $(II)^a$ may be converted to -COL wherein L represents a leaving group by, for example, halogenation using thionyl chloride.

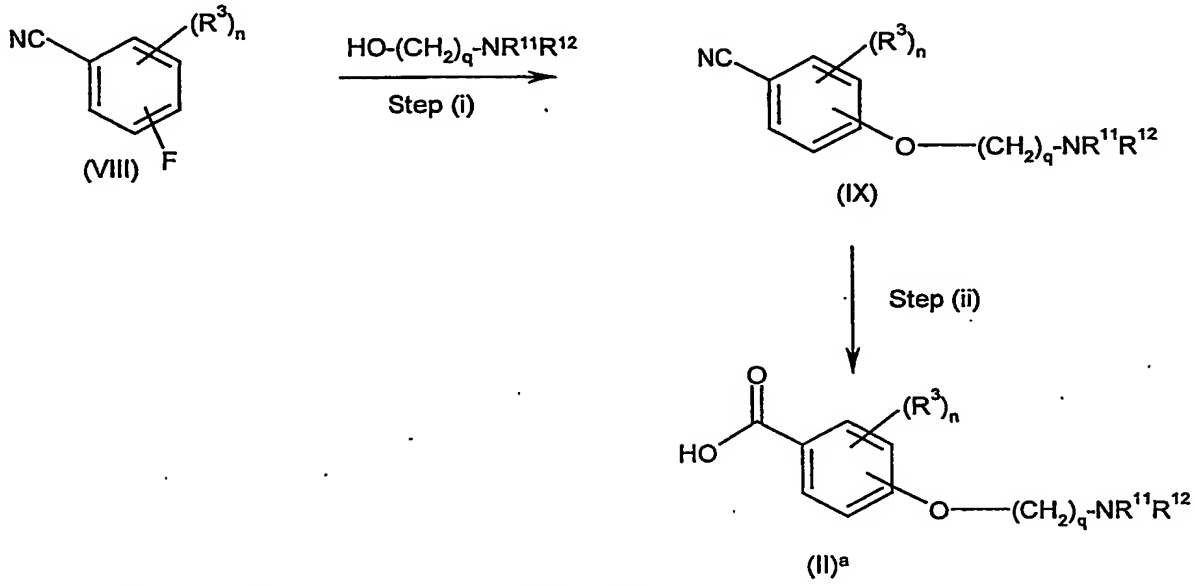
Step (i) typically comprises reaction of a compound of formula (V) with a suitable alkylating agent such as 1-bromo-3-chloropropane in a suitable solvent such as acetone in the presence of potassium carbonate.

Step (ii) typically comprises treatment of a compound of formula (VI) with an amine of formula $HNR^{11}R^{12}$.

Step (iii) comprises a deprotection reaction which may be performed for example under acidic conditions with hydrochloric acid.

Compounds of formula (IV) may be prepared by hydrolysing a compound of formula (VI) as defined above under suitable conditions (eg. under acidic conditions with HCl), suitably activated (eg. by conversion into the acid chloride with thionyl chloride), followed by treatment with a compound of formula (III) as defined above.

Compounds of formula (II) wherein R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ may also be prepared in accordance with the following procedure:



wherein R^3, n, q, R^{11} and R^{12} are as defined above.

Step (i) typically comprises reaction of a compound of formula (VIII) in the presence of a suitable base such as sodium hydride in an appropriate solvent such as dimethylsulfoxide or N,N-dimethylformamide.

Step (ii) typically comprises a hydrolysis reaction for example under acidic conditions using hydrochloric acid.

Compounds of formula (IV) may be prepared using an analogous procedure using HO-$(CH_2)_q$-L^2, wherein q is as defined above and L^2 represents an OH group or a group convertible to a leaving group.

Compounds of formula (II) wherein R^4 represents a group of formula (i) may be prepared in a similar manner to the procedure shown above.

Compounds of formula (III), (V) and (VIII) are either known in the literature or can be prepared by analogous methods.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, Parkinson's disease, multiple sclerosis, stroke and sleep disorders

including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular neurodegenerative disorders including Alzheimer's disease.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be

frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

Ethyl 4-(3-Piperidin-1-ylpropoxy)benzoate (D1)

A stirred mixture of ethyl 4-(3-chloropropoxy)benzoate (4.73g) (D.A.Walsh *et al* J. Med. Chem. 1989, **32**(1), 105), piperidine (2.9ml), sodium carbonate (3.1g) and potassium iodide (162mg) in 1-butanol (50ml) was heated at 105° C for 16h. The reaction was cooled to rt, diluted with EtOAc (100ml), washed with water (3x50ml), saturated brine (50ml), dried ($MgSO_4$) and evaporated to give the title compound (D1) (6.88g). MS electrospray (+ion) 292 (MH^+). ^1H NMR δ ($CDCl_3$): 7.98 (2H, d, J=8.8Hz), 6.90 (2H, d, J=8.8Hz), 4.34 (2H, q ,J=7.5Hz), 4.06 (2H, t, J=6.3Hz), 2.46 (4H, m), 2.00 (2H, m), 1.50 (6H, m), 1.38 (3H, t, J=7.5Hz).

Description 2

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2)

A solution of ethyl 4-(3-piperidin-1-ylpropoxy)benzoate (D1) (1.4g) in concentrated hydrochloric acid (15ml) was heated under reflux for 1h, cooled and evaporated to give the title compound (D2) (1.02g). MS electrospray (+ion) 264 (MH^+). ^1H NMR δ (DMSO-d6): 10.59 (1H, s), 10.25 (1H, s), 7.90 (2H, d, J=9Hz), 7.02 (2H, d, J=9Hz), 4.14 (2H, t, J=6Hz), 3.05-3.52 (4H, m), 2.91 (2H, m), 2.20 (2H, m), 1.25-1.91 (6H, m).

Description 3

4-(3-Piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3)

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (0.23g) in thionyl chloride (5ml) was heated under reflux for 1h. The reaction mixture was then evaporated to a

minimum and co-evaporated from DCM (3 x 10ml) to give the title compound (D3) as a white powder (0.24g).

Description 4

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzonitrile (D4)

4-Fluoro-2-trifluoromethyl-benzonitrile (1.20g) was dissolved in THF (20 ml) and 3-piperidin-1-yl-propan-1-ol (0.91 ml) was added. The reaction was cooled to 0°C and potassium hexamethyldisilazide (0.5M solution in toluene; 12.72 ml) was added dropwise. The reaction was stirred at rt overnight, then diluted with ethyl acetate (50 ml) and partitioned with aqueous 1N HCl (50 ml). The aqueous layer was washed with ethyl acetate (50 ml), then basified to pH 8.0 with sodium hydrogen carbonate and extracted with ethyl acetate (3x75 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the title compound (D4) as a clear oil which crystallised on standing (0.80g).

Description 5

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoic acid (D5)

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzonitrile (D4) (0.80 g) was dissolved in conc. HCl (20 ml) and heated at 135°C for 24 h. Concentrated sulfuric acid (10 ml) was added and the reaction heated at 135°C for 36h. The reaction mixture was then evaporated to a minimum and treated with 12.5 N sodium hydroxide solution until pH 12 was obtained. The mixture was filtered and the filtrate evaporated to a minimum. Conc. HCl was then added until pH 1. The mixture was evaporated and the solid residue was extracted several times with methanol. The combined extracts were evaporated to give the title compound (D5) as a white solid (0.90g).

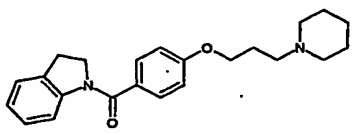
Description 6

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoyl chloride (D6)

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoic acid (D5) (0.9 g) was heated at reflux in thionyl chloride (20 ml) for 2h. The reaction mixture was evaporated to a minimum then co-evaporated with DCM (3x) to give the title compound (D6) as a white solid (1.0g)

Example 1

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]indoline hydrochloride (E1)

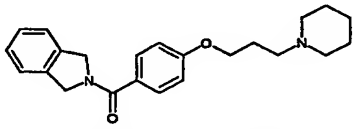


A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) in thionyl chloride (4ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride

was re-evaporated from DCM (2x3ml). The residue was redissolved in DCM (5ml) and triethylamine (0.21ml) and added to a stirred solution of indoline (54mg) in DCM (2ml) at rt. The mixture was stirred for 1h, washed with saturated sodium hydrogen carbonate solution (5ml), water (3x5ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel, step gradient 4-8% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E1) (126mg). MS electrospray (+ion) 365 (MH^+). ^1H NMR δ (DMSO-d6): 10.21 (1H, s), 6.95-7.81 (8H, m), 4.14 (2H, t, J=6Hz), 4.04 (2H, t, J=8Hz), 2.80-3.00 (6H, m), 2.88 (2H, m), 2.20 (2H, m), 1.30-1.85 (6H, m).

Example 2

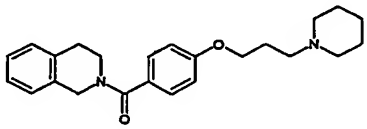
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]isoindoline hydrochloride (E2)



4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) was converted to the title compound (E2) by reaction with isoindoline (54mg) using the method described in Example 1 (E1) (yield = 198mg). MS electrospray (+ion) 365 (MH^+). ^1H NMR δ (DMSO-d6): 10.33 (1H, s), 7.62 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.8Hz), 7.31 (4H, m), 4.86 (2H, s), 4.82 (2H, s), 4.13 (2H, t, J=6.5Hz), 2.80-3.52 (6H, m), 2.21 (2H, m), 1.30-1.85 (6H, m).

Example 3

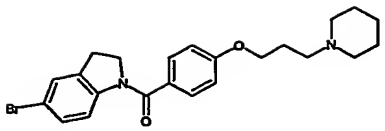
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,4-dihydro-1H-isoquinoline hydrochloride (E3)



4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (299mg) was converted to the title compound (E3) by reaction with 1,2,3,4-tetrahydroisoquinoline (133mg) using the method described in Example 1 (E1) (yield = 376mg). MS electrospray (+ion) 379 (MH^+). ^1H NMR δ (DMSO-d6): 9.89 (1H, s), 7.00-7.45 (8H, m), 4.69 (2H, s), 4.11 (2H,t, J=6Hz), 3.7 (2H, m), 3.46 (2H, m), 3.18 (2H, m), 2.89 (4H, m), 2.18 (2H, m), 1.30-1.87 (6H, m).

Example 4

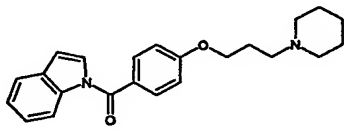
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-bromoindoline hydrochloride (E4)



4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (299mg) was converted to the title compound (E4) by reaction with 5-bromoindoline (198mg) using the method described in Example 1 (E1) (yield = 372mg). MS electrospray (+ion) 443, 445 (MH^+). ^1H NMR δ (DMSO-d6): 10.05 (1H, s), 7.01-7.82 (7H, m), 4.11 (2H, t, J=6Hz), 4.06 (2H, m), 3.46 (2H, m), 3.19 (2H, m), 3.09 (2H, m), 2.21 (2H, m), 1.30-1.87 (6H, m).

Example 5

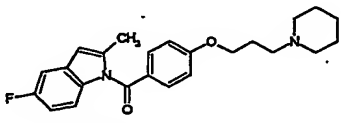
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]indole hydrochloride (E5)



A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) in thionyl chloride (4ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x3ml). The residue was redissolved in DMF (3ml) and added to an ice-cold stirred solution of indole (59mg) and sodium hydride (40mg of a 60% dispersion in oil)in DMF (2ml). The mixture was stirred for 1h then 2h at rt. Methanol (2ml) was added and the mixture evaporated. The residue was chromatographed (silica gel, step gradient 4-8% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E5) (72mg). MS electrospray (+ion) 363 (MH^+). ^1H NMR δ (DMSO-d6): 10.30 (1H, s), 6.75-8.22 (10H, m), 4.20 (2H, t, J=6Hz), 2.80-3.55 (6H, m), 2.25 (2H, m), 1.25-1.91 (6H, m).

Example 6

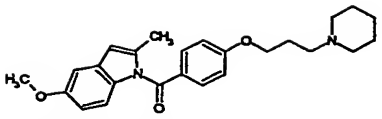
5-Fluoro-2-methyl-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-indole hydrochloride (E6)



The title compound (E6) was prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and 5-fluoro-2-methyl-indole using the method described in Example 5 (E5).

Example 7

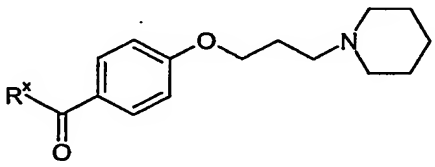
5-Methoxy-2-methyl-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-indole hydrochloride (E7)

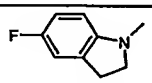
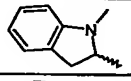
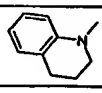


The title compound (E7) was prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and 5-methoxy-2-methyl-indole using the method described in Example 5 (E5).

Examples 8-10 (E8-10)

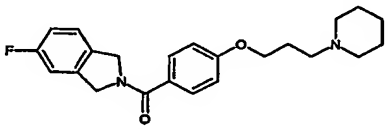
Examples 8 – 10 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 1 (E1) and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E8		383 $[M+H]^+$
E9		379 $[M+H]^+$
E10		379 $[M+H]^+$

Example 11

N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-4-fluoroisoindoline hydrochloride (E11)

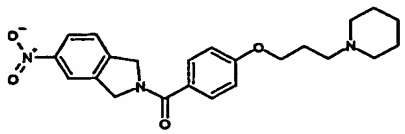


A stirred mixture of 4-fluoroisoindoline (183mg) (W. Adcock et al Aust J Chem 1976, 29, 2571) and diethylaminoethylpolystyrene (626mg, 3.2 mmol/g) in DCM (10ml) at rt was treated with 4-(3-piperidin-1-ylpropoxy)-benzoyl chloride hydrochloride (223mg) (D3). After 1h the reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM)]. Fractions containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (4M solution in dioxan) and then evaporated. The residue was triturated with acetone, filtered, washed with acetone and dried to yield the title compound (E11) (80mg). MS electrospray (+ion) 383 (MH^+). ^{1}H NMR δ (DMSO-d6): 10.21 (1H, s), 7.61

(2H, d, J=8.8Hz), 7.05-7.50 (3H, m), 7.01 (2H, d, J=8.8Hz), 4.81 (4H, m), 4.13.(2H, t, J=6 Hz), 3.46 (2H, m), 3.15 (2H, m), 2.88 (2H, m), 2.21 (2H, m), 1.28-1.92 (6H, m).

Example 12

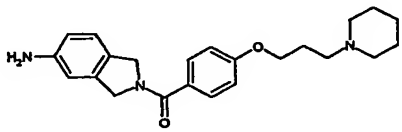
N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-4-nitroisoindoline hydrochloride (E12)



An ice cold stirred mixture of 4-nitroisoindoline (2.27g) (Fraenkel, Chem Ber 1900, 33, 2811) and 4-(3-piperidin-1-ylpropoxy)-benzoyl chloride hydrochloride (3.35g) (D3) in DCM (50ml) was treated dropwise with triethylamine (5.56 ml). The reaction mixture was allowed to gain rt, stirred for 1h then washed with saturated sodium hydrogen carbonate solution (50ml), water (3x50ml), brine (50ml),dried ($MgSO_4$) and evaporated. Chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM)] afforded the free base (2.92g). A sample (47mg) in DCM (2ml) was treated with excess 4M HCl in dioxan and evaporated to give the title compound (E12) (51mg) . MS electrospray (+ion) 410 (MH^+). ^1H NMR δ (DMSO-d6): 10.20 (1H, s), 8.25 (2H, m), 7.62 (3H, m), 7.03 (2H, d, J=8.8Hz), 4.95 (4H, m), 4.14.(2H,t, J=6 Hz), 3.45 (2H, m), 3.20 (2H, m), 2.90 (2H, m), 2.20 (2H, m), 1.28-1.92 (6H, m).

Example 13

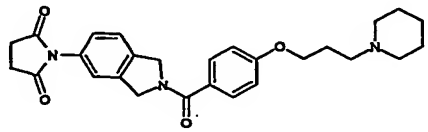
N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-4-aminoisoindoline hydrochloride (E13)



A stirred solution of N-[4-(3-piperidin-1-ylpropoxy)-benzoyl]-4-nitroisoindoline (E12) (0.5g) in THF (50ml) was treated with titanium (III) chloride (5.63ml of a 30% w/v solution in hydrochloric acid). After 3h EDTA (2.85g) and water (100ml) were added and the mixture stirred for 15 min. The mixture was made basic with potassium carbonate and extracted with DCM (2x75ml). The combined extracts were dried ($MgSO_4$) and evaporated. Chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM)] afforded the free base (430mg). A sample (25mg) in DCM (2ml) was treated with excess 4M HCl in dioxan and evaporated to give the title compound (E13) (26mg) . MS electrospray (+ion) 380 (MH^+). ^1H NMR δ (DMSO-d6): 10.41 (1H, s), 9.80 (2H, bs), 7.61 (2H, d, J=8.5Hz), 7.09-7.51 (3H, m), 7.03 (2H, d, J=8.5Hz), 4.85 (4H, m), 4.10.(2H, t, J=6 Hz), 3.45 (2H, m), 3.19 (2H, m), 2.91 (2H, m), 2.21 (2H, m), 1.28-1.95 (6H, m).

Example 14

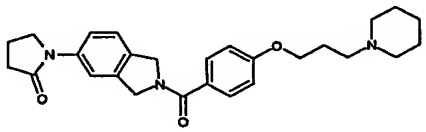
N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-4-(1-succinimido)-isoindoline hydrochloride (E14)



A stirred mixture of succinic anhydride (79mg) and N-[4-(3-piperidin-1-ylpropoxy)-benzoyl]-4-aminoisoindoline hydrochloride (E13) (150mg) were fused at 150°C for 2h. The mixture was cooled to rt and partitioned between EtOAc (10ml) and saturated sodium hydrogen carbonate solution (10ml). The organic layer was washed with water (2x10ml), brine (10ml), dried ($MgSO_4$) and evaporated. The residue was dissolved in DCM, treated with excess 4M HCl in dioxan and evaporated. Crystallisation from EtOH / diethyl ether gave the title compound (E14) (90mg) . MS electrospray (+ion) 462 (MH^+). ^1H NMR δ (DMSO-d6): 10.15 (1H, s), 7.63 (2H, d, J=8.5Hz), 7.08-7.54 (3H, m), 7.02 (2H, d, J=8.5Hz), 4.87 (4H, m), 4.13.(2H, t, J=6 Hz), 3.09-3.52 (8H, m) , 2.91 (2H, m), 2.21 (2H, m), 1.30-1.88 (6H, m).

Example 15

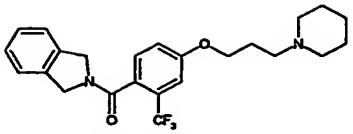
N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-4-(2-oxo-pyrrolidin-1-yl)-isoindoline hydrochloride (E15)



A stirred mixture of diethylaminomethyl polystyrene (247mg, 3.2mmol/g) and N-[4-(3-piperidin-1-ylpropoxy)-benzoyl]-4-aminoisoindoline hydrochloride (E13) (150mg) in DCM (5ml) at rt was treated with 4-bromobutanoyl chloride (0.05ml) for 30 mins. The mixture was filtered and evaporated. The residue was redissolved in DMF (5ml) and treated with sodium hydride (18mg of a 60% suspension in mineral oil) and stirred for 2h. A further portion of sodium hydride (18 mg) was added and the mixture stirred for 1h. The reaction was partitioned between EtOAc (10ml) and saturated sodium hydrogen carbonate solution (10ml). The organic layer was washed with water (2x10ml), brine (10ml), dried ($MgSO_4$) and evaporated. After chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM)] fractions containing the required product were evaporated, then redissolved in DCM, treated with excess 4M HCl in dioxan and evaporated. Crystallisation from EtOH / diethyl ether afforded the title compound (E15) (77mg) . MS electrospray (+ion) 448 (MH^+). ^1H NMR δ (DMSO-d6): 10.15 (1H, s), 7.60 (4H, m), 7.34 (1H, m), 7.0 (2H, d, J=8.5Hz), 4.80 (4H, m), 4.13.(2H, t, J=6 Hz), 3.80 (2H, m) , 3.05-3.58 (6H, m), 2.91 (2H,m), 2.21 (2H, m), 2.06 (2H, m), 1.28-1.90 (6H, m).

Example 16

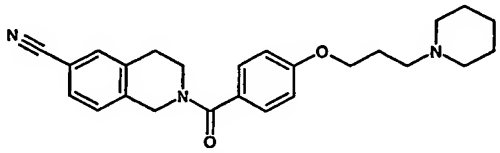
N-[4-(3-Piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]isoindoline hydrochloride (E16)



A solution of 4-(3-piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoyl chloride (D6) (150 mg) in DCM (10ml) was added to isoindoline (0.046ml) and diethylaminomethyl polystyrene (0.60g; 3.2mmol/g). The mixture was stirred for 16h, then loaded directly onto a silica column and eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM. The isolated free base was dissolved in DCM (5ml) and treated with 4N HCl/dioxane solution (1 ml) with stirring for 10 min. The mixture was concentrated, and the residue co-evaporated with toluene (3x10ml) and then dried at 50°C under high vacuum for 16h to yield the title compound (E16) as a beige solid (0.094g). MS electrospray (+ion) 433 (MH^+). ^1H NMR δ (DMSO-d6): 9.96 (1H, s), 7.63 (1H, d, J=8.36 Hz), 7.46-7.23 (6H, m), 4.82 (2H, s), 4.47 (2H, s), 4.20 (2H, t, J=5.88Hz), 3.47 (2H, m), 3.19 (2H, m), 2.87 (2H, m), 2.20 (2H, m), 1.80-1.38 (6H, m).

Example 17

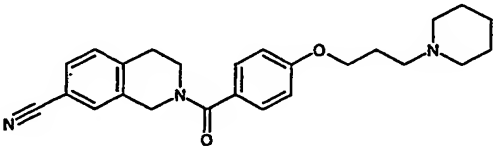
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6-cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride (E17)



The title compound was prepared from 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.20g) and 6-cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride (WO98/50363) (0.15g) using the procedure described for Example 1 and isolated as a white solid (0.13g). MS electrospray (+ion) 404 (MH^+). ^1H NMR δ (DMSO-d6): 10.20 (1H, s), 7.69 (1H, s), 7.65 (1H, d, J=7.5Hz), 7.45 (3H, m), 7.02 (2H, d, J=8.6Hz), 4.76 (1H, s), 4.11 (1H, t, J=5.9), 3.68 (2H, m), 3.44 (2H, m), 3.17 (2H, m), 2.90 (4H, m), 2.19 (2H, m), 1.78-1.37 (6H, m).

Example 18

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride (E18)

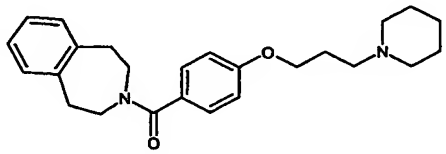


A solution of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.14g) in DCM (10ml) was added to 7-cyano-1,2,3,4-tetrahydroisoquinoline (WO98/50364) (0.08g) and diethylaminomethyl polystyrene (0.6g, 3.2mmol/g). The mixture was stirred for 16h then loaded directly onto a silica column and eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM. The isolated free base was dissolved in DCM (5ml)

and treated with 4N HCl/dioxane solution (1 ml) with stirring for 10min. The mixture was concentrated and the residue co-evaporated with toluene (3x10ml) then crystallised from ethanol/diethyl ether, and dried at 80°C under high vacuum for 16h to yield the title compound (E18) as a beige solid (0.03g). MS electrospray (+ion) 404 (MH^+). ^1H NMR δ (DMSO-d6): 9.91 (1H, s), 7.85 (1H, m), 7.65 (1H, d, J=7.9Hz), 7.42 (3H, m), 7.02 (2H, d, J=8.6), 4.73 (2H, s), 4.11 (2H, t, J=5.9 Hz), 3.68 (2H, m), 3.44 (2H, m), 3.17 (2H, m), 2.93 (4H, m), 2.20 (2H, m), 1.91-1.41 (6H, m).

Example 19

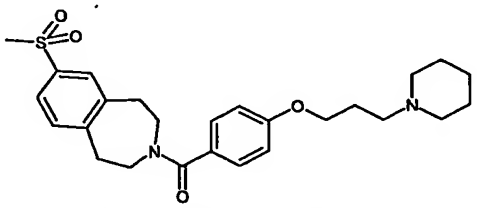
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E19)



The title compound was prepared from 4-(3-piperidin-1-ylpropoxy) benzoyl chloride hydrochloride (D3) (0.20g) and 2,3,4,5-tetrahydro-1*H*-3-benzazepine (WO00/21951) (0.89g) using the procedure described for Example 1 and isolated as a white solid (0.16g). MS electrospray (+ion) 393 (MH^+). ^1H NMR δ (DMSO-d6): 9.68 (1H, s), 7.34 (2H, d, J=6.8Hz), 7.14 (4H, m), 7.00 (2H, d, J=6.8Hz), 4.10 (2H, t, J=5.9Hz), 3.81-3.45 (6H, m), 3.17 (2H, m), 2.90 (6H, m), 2.17 (2H, m), 1.83-1.37 (6H, m).

Example 20

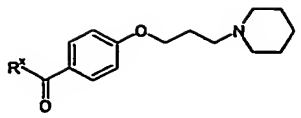
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-methanesulfonyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (E20)

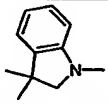
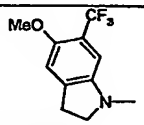
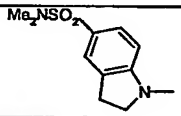
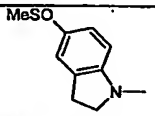
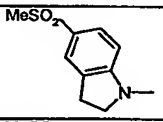
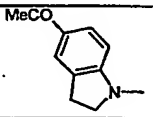
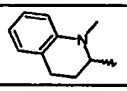
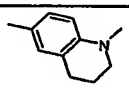
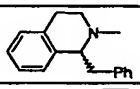
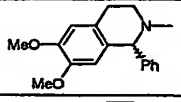
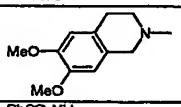
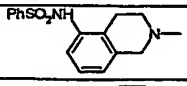
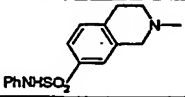
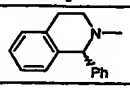


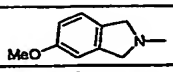
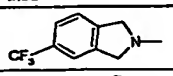
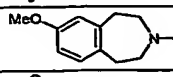
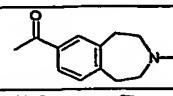
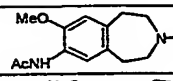
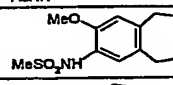
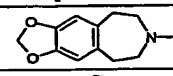
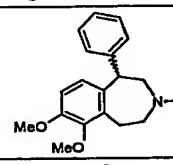
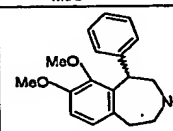
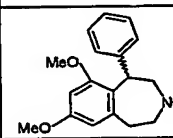
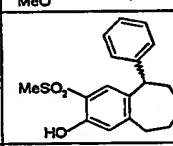
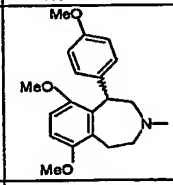
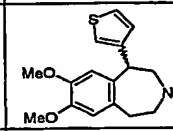
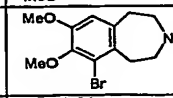
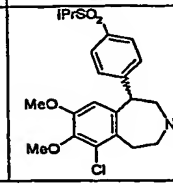
The title compound was prepared from 4-(3-piperidin-1-ylpropoxy) benzoyl chloride hydrochloride (D3) (0.20g) and 7-methanesulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (WO00/21951) (0.17g) using the procedure described for Example 1 and isolated as a white solid (0.24g). MS electrospray (+ion) 471 (MH^+). ^1H NMR δ (DMSO-d6): 9.83 (1H, s), 7.71 (2H, m), 7.44 (1H, s), 7.35 (2H, d, J=8.5Hz), 7.01 (2H, d, J=8.6Hz), 4.11 (2H, t, J=5.9Hz), 3.71-3.45 (6H, m), 3.18 (6H, m), 3.05 (3H, s) 2.87 (2H, m), 2.20 (2H, m), 1.83-1.37 (6H, m).

Examples 21-49 (E21-E49)

Examples 21 – 49 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 1 (E1) and displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E21		$[M+H]^+$ 393
E22		$[M+H]^+$ 463
E23		$[M+H]^+$ 472
E24		$[M+H]^+$ 427
E25		$[M+H]^+$ 443
E26		$[M+H]^+$ 407
E27		$[M+H]^+$ 393
E28		$[M+H]^+$ 393
E29		$[M+H]^+$ 469
E30		$[M+H]^+$ 515
E31		$[M+H]^+$ 439
E32		$[M+H]^+$ 534
E33		$[M+H]^+$ 534
E34		$[M+H]^+$ 455

E35		$[M+H]^+$ 395
E36		$[M+H]^+$ 433
E37		$[M+H]^+$ 424
E38		$[M+H]^+$ 434
E39		$[M+H]^+$ 480
E40		$[M+H]^+$ 516
E41		$[M+H]^+$ 437
E42		$[M+H]^+$ 530
E43		$[M+H]^+$ 530
E44		$[M+H]^+$ 530
E45		$[M+H]^+$ 564
E46		$[M+H]^+$ 559
E47		$[M+H]^+$ 536
E48		$[M+H]^+$ 532
E49		$[M+H]^+$ 669

Preparation of precursors

Certain precursors referred to in the preparation of the above Examples were prepared from the following references:

Substituted isoindolines: 4-Fluoroisoindoline (W. Adcock et al., Aust J Chem 1976, 29, 2571), 4-methoxyisoindoline and 4-trifluoromethoxyisoindoline (N E Austin et al., Bioorg Med Chem Lett., 2001, 11, 5, 685), 4-nitroisoindoline (Fraenkel, Chem Ber 1900, 33, 2811).

Substituted 1,2,3,4-tetrahydroisoquinolines: 6-cyano-1,2,3,4-tetrahydroisoquinoline (WO9850363, SmithKline Beecham), 7-cyano-1,2,3,4-tetrahydroisoquinoline (WO9850364, SmithKline Beecham).

Substituted benzazepines: 7-cyano-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 7-acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and 7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (WO0021951, SmithKline Beecham).

Abbreviations

Boc	tertbutoxycarbonyl
EtOAc	ethyl acetate
h	hour
DCM	dichloromethane
MeOH	methanol
rt	room temperature
DCC	dicyclohexylcarbodiimide
DMF	dimethylformamide

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as

described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α *E. coli* host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the *sh ble* gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g

for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10µl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller. The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

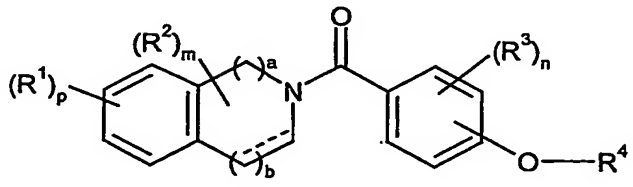
The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compounds of Examples E1-E49 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values >7.5. In particular, Examples E1-2, E4-12, E15-19, E21-31, E33, E35-36, E38-39, E41-42, E44-45 and E47 exhibited pK_b values > 8.5.

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 independently represent halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, aryl, heteroaryl, heterocyclyl, arylC_{1-6} alkyl, heteroarylC_{1-6} alkyl, heterocyclylC_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, -CO-aryl, -CO-heterocyclyl, -CO-heteroaryl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylaminosulfonyl, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $NR^{15}R^{16}$, -NR^{15}CO-aryl, -NR^{15}CO-heterocyclyl, -NR^{15}CO-heteroaryl, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl;

wherein said aryl, heteroaryl and heterocyclyl groups of R^1 and R^2 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different and which are selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, CF_3, OCF_3, CN, C_{1-6} alkanoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylamido or C_{1-6} alkylsulfonamido;

a and b independently represent 0, 1 or 2;

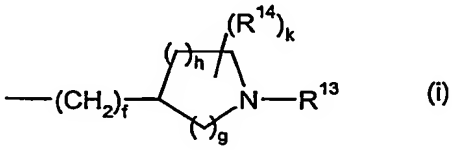
------ is a single or double bond;

R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

m and n independently represent 0, 1 or 2;

p represents an integer from 0 to 3, such that when p is an integer greater than 1, two R^1 groups may instead be linked to form a heterocyclyl group;

R^4 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group optionally substituted by one or two R^{17} groups;
R^{13} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl or heterocyclyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, OH, diC_{1-6} alkylamino or C_{1-6} alkoxy;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or solvates thereof.

2. A compound according to claim 1 which is a compound of formula E1-E49 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of Alzheimer's disease.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.